**Impact of infliximab and etanercept biosimilars on biological disease modifying antirheumatic drugs utilisation and NHS budget in UK**

Mohammed I Aladul1,2, Raymond W Fitzpatrick1, Stephen R Chapman1\*

1 School of Pharmacy, Keele University, Hornbeam Building, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

2 School of Pharmacy, University of Mosul, Mosul, Nineveh, Iraq.

\* Correspondence to: Stephen R Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: s.r.chapman@keele.ac.uk

ORICD: 0000-0002-0326-7742

**Running heading:** Impact of biosimilars introduction in rheumatology

**Abstract**

***Objective:*** Biological disease modifying antirheumatic drugs (bDMARDs) are effective but expensive options for treating rheumatoid arthritis. The introduction of infliximab and etanercept biosimilars present a significant potential cost saving in a financially constrained health system such as the National Health Service (NHS) in the UK. This study examines the impact of the introduction of infliximab and etanercept biosimilars on the utilisation of bDMARDs and subsequent budget impact.

***Methods:*** Interrupted time series analysis of secondary care utilisation data in rheumatology specialities from the DEFINE database, between March 2014 and February 2017.

***Results:*** The cumulative cost savings from the introduction of infliximab and etanercept biosimilars was £38.8 million in two years. There was a statistically significant increase in average monthly utilisation of bDMARDs for; adalimumab 0.48%, certolizumab pegol 1.90%, golimumab 3.06%, abatacept 2.97% and tocilizumab 2.24%, but not for etanercept. In contrast, the overall utilisation of infliximab decreased slightly on by an average of 0.03% per month. The introduction of infliximab biosimilar negatively affected the monthly utilisation of branded infliximab significantly. Similarly, the introduction of etanercept biosimilar negatively affected the monthly utilisation of branded etanercept significantly.

***Conclusions:*** The introduction of bDMARDs biosimilars has resulted in considerable cost savings to the NHS, with the branded products reducing their prices in response to the availability of less expensive biosimilars and competition between the biosimilars themselves. Our results also suggest that when a biosimilar is available for a directly comparable branded molecule, price is the key influencing factor in the prescribing of a specific product.

**Key points**

* Previous studies predicted a considerable budget impact from the introduction of infliximab and etanercept biosimilars.
* This study compared estimated budget impact with real life budget impact in rheumatology specialities in UK hospitals.
* This study analysed the impact of the introduction of infliximab and etanercept biosimilars on the utilisation of branded biological disease modifying antirheumatic agents in UK hospitals.

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1. **Introduction**

Biological disease modifying antirheumatic drugs (bDMARDs) are effective, but, expensive options for treating autoimmune disorders including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PA) as recommended by the National Institute of Health and Clinical Excellence (NICE) [1]. bDMARDs have a considerable impact on healthcare budgets. In 2015, six of the top ten blockbuster medicines in Europe were bDMARDs inhibitors. Global expenditure on infliximab, etanercept and adalimumab accounted for £24 billion in 2015 [2, 3], and in 2015/16 adalimumab, etanercept and infliximab were in the top 5 by spend of NICE approved medicines in England with a total cost of just over £825 million (in all sectors) which represents just under 5% of the total medicines expenditure [4]. Adalimumab, etanercept, infliximab and other bDMARDs have a comparable efficacy and safety profile [5, 6]. These agents differ in their frequency, route of administration, the extent to which they can be used as monotherapy or must be used in combination with methotrexate, indications and annual cost. Table 1 summarises the specifications of available bDMARDs in UK.

In UK, around 10 million people have a form of arthritis, with a prevalence of (0.8%), which equates to 700,000 patient having RA and around 12,000 children suffer from juvenile idiopathic arthritis (JIA) [7]. The prevalence of AS is 0.13% [8] and 0.19% for PA [9].

The practice of switching between bDMARDs has become well established for patients with RA who have had an inadequate response or intolerable adverse events [10, 11], and has been recommended by NICE, the European League Against Rheumatism (EULAR) and the Consensus Group on Advances in Targeted Therapy [12-14]. Studies have also reported switching between bDMARDs for reasons other than clinical need, such as patient access schemes or switching from infliximab to etanercept or adalimumab for the convenience of the subcutaneous route of administration and/or home (self) administration [15, 16]. Relative prices of individual bDMARDs vary by acquisition costs, direct medical and non-medical costs associated with administration (intravenous infusion administration of infliximab in hospitals versus subcutaneous administration by nurse at hospitals or home for adalimumab or etanercept) [17]. Thus, switching may also be encouraged by health service commissioners, to realise cost savings since in the NHS in the UK these commissioners are responsible for the medicines budget and managing the cost pressures. Drugs given in hospitals are subject to value-added tax (VAT) (20%) whereas those delivered via home care are exempted from VAT [18].

Table 1 Summary of product specifications [19, 1]:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Molecule**  | **Administration**  | **Monotherapy** | **Frequency** | **Presentation**  | **EU. Approval** | **Indications in rheumatic disorders** | **\*Annual cost** |
| **Infliximab** | I.V. infusion | No | Every 4-8 weeks | Vial  | Sep. 1999 | RA, AS, PA  | £10,070 for the first year and £8812 for subsequent years\*\*£9063 for the first year and £7930 for subsequent years |
| **Etanercept** | S.C. | Yes | Twice- once weekly | Prefilled pen, prefilled syringe and vial | Jun. 2000 | RA, axSpA, PA, JIA, AS, nr-axSpA | £9295 |
| **Adalimumab** | S.C. | Yes | Every 2 weeks | Prefilled pen, prefilled syringe and vial | Sep. 2003 | RA, axSpA, PA, JIA | £9155 |
| **Abatacept** | I.V. infusion or S.C. | No | I.V. Every 4 weeksS.C. Once weekly | Prefilled pen, prefilled syringe and vial | May 2007 | RA | £12,700 for the first year and £11,793 for subsequent years |
| **Certolizumab pegol** | S.C.  | Yes | Every 2 weeks | Prefilled pen, prefilled syringe | Jun. 2009 | RA, axSpA, PA | £10,367 for the first year and £9295 for subsequent years |
| **Tocilizumab** | I.V. infusion or S.C. | Yes | Every 4 weeks | Prefilled syringe and vial | Sep. 2009 | RA | £9318 |
| **Golimumab** | S.C. | No | Every month | Prefilled pen, prefilled syringe | Oct. 2009 | RA, axSpA, PA | £9155 |

\*Annual cost according to the National Institute for Health Excellence (Costs may vary in different settings because of negotiated procurement discounts). EU, European Union. I.V., intravenous. S.C., subcutaneous. RA, Rheumatoid arthritis. JIA, Juvenile idiopathic arthritis. PA, Psoriatic arthritis. axSpA, Axial spondyloarthritis. AS, Ankylosing spondylitis. nr-axSpA, Non-radiographic axial spondyloarthritis. \*\* Annual cost of infliximab biosimilar (Remsima® or Inflectra®).

Infliximab and etanercept were the first bDMARDs to lose patent protection and have had competition from biosimilars in Europe since 2013 [20]. The lower cost of biosimilars (Table 2) presents a significant potential cost saving in a financially constrained health system such as the NHS [21]. Thus, in theory a lower acquisition cost potentially removes one barrier to prescribing biologics.

Since adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab are recommended options for treating RA, it was anticipated that the introduction of less expensive biosimilars of infliximab and etanercept, would provoke switching/substitution between these agents. This study aims to determine the impact of the introduction of infliximab and etanercept biosimilars on the utilisation of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab in UK hospitals and the subsequent budget impact.

1. **Methods**
	1. **Data source**

The study was a retrospective analysis of UK secondary care utilisation of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab in rheumatology specialities. Monthly secondary care data were taken from the DEFINE Software from January 2014–February 2017. The DEFINE Software is a NHS prescribing database of medicines usage covering over 90% of acute NHS hospitals as well as Specialist Centres and Mental Health Trusts throughout the UK [22]. Data were at gross national level not at institutional or patient level. The volume comparator was the defined daily dose (DDD) which is defined by the WHO as the mean maintenance daily dose of a medicine for its principal indication in adults. The DDD index for adalimumab is 2.9 mg, etanercept is 7 mg, infliximab is 3.75 mg, certolizumab pegol is 14 mg, golimumab is 1.66 mg abatacept is 27 mg and tocilizumab is 20 mg [23]. Secondary care data within the DEFINE database were already converted into DDDs. Prices of the individual preparations were expressed as price per DDD (£/DDD). Secondary care prices were the average net prices for different trusts throughout the UK including VAT.

* 1. **Statistical analysis**

**2.2.1. Expenditure and savings**

Annual usage and expenditure on each medicine for 2015/16 and 2016/17 was taken from the DEFINE Software [22]. This usage was then multiplied by the price of the branded product before the introduction of biosimilars to calculate what the expenditure would have been without biosimilars. The actual cost for infliximab and etanercept (branded and biosimilar) over this period was then deducted from this estimated expenditure to calculate the actual savings to the NHS. The estimated savings in previous studies (in euros) [24-31] were converted to British pounds for reason of comparison with savings in UK at a rate of 1 Euro = £0.84506.

**2.2.2. Overall utilisation of bDMARDs**

bDMARDs utilisation were examined over the period March 2014 - February 2017. Linear regression analyses were used with time (monthly) as the independent variable and utilisation in DDD as the dependent variable. The regression coefficient values were divided by the baseline utilisation DDD (in March 2014) to calculate the average monthly percentage increase or decrease in utilisation of bDMARDs.

* + 1. **Segmented regression of interrupted time series**

Segmented regression of interrupted time series calculates the changes in pre and post intervention levels (the level represents the Y-axis intercept for the first segment and the value immediately following each change point at which successive segments join) and trend (the trend represents the rate of change of a measure (i.e. the slope)) of each segment of the series. A change in level, e.g. a jump or drop in the outcome after the intervention, constitutes an abrupt intervention effect. A change in trend is defined by an increase or decrease in the slope of the segment after the intervention as compared with the segment preceding the intervention. A change in trend represents a gradual change in the value of the outcome during the segment [32].

Segmented regression analysis determines whether the intervention or other factors were responsible for the observed change if any [32]. Therefore, interrupted time series analysis is considered as the most robust quasi-experimental design in drug utilisation studies. The strength of this design lies in its ability to evaluate the effects of interventions for which it is difficult to identify an appropriate control group [33].

* + 1. **Impact of biosimilars introduction on the trend of utilisation of originator bDMARDs**

Trends in the utilisation of branded and biosimilar bDMARDs in UK were evaluated. A segmented regression analysis of interrupted time series model was used to examine the changes in utilisation patterns of these medicines before and after the introduction of biosimilar versions of infliximab and etanercept [32]. The change in utilisation of bDMARDs was assessed by two parameters, level (β2 and β4) and trend (β3 and β5). The following segmented regression analysis equation was applied to each individual study outcome measure:

Yt = β0 + β1 × time + β2 × introduction of infliximab biosimilars + β3 × time after introduction of infliximab biosimilars + β4 × introduction of etanercept biosimilar + β5 × time after introduction of etanercept biosimilar + et.

Yt is the monthly outcome measure in DDDs. Time was a continuous variable referring to time in months, ranging from 1 to 36 from the start to the end of the study period. The introduction of infliximab biosimilars was a dichotomous variable (0 before March 2015; 1 since March 2015). Time after introduction of infliximab biosimilars was a continuous variable beginning in March 2015. Introduction of etanercept biosimilar was a dichotomous variable (0 before March 2016; 1 since March 2016). Time after introduction of etanercept biosimilar was a continuous variable beginning in March 2016. β0 and β1 represent the intercept and trend over time during the pre-intervention period, respectively. β2 represents the change in the level at the time of introduction of infliximab biosimilars, β3 represents the trend change in the slope after introduction of infliximab biosimilars, both compared to those in the pre-intervention period. β4 represents the change in level at the time of introduction of etanercept biosimilar and β5 represents the change in slope after introduction of etanercept biosimilar. et represents the error term. While segmented regression models primarily have a linear specification, polynomial and non-linear regression can be used if the data exhibit non-linear patterns. We conducted all statistical analysis using STATA MP13.

1. **RESULTS**
	1. **Prices, utilisation and expenditure**

Secondary care prices of branded adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab did not change before the introduction of infliximab and etanercept biosimilars in March 2015 and 2016 respectively. Following the introduction of infliximab and etanercept biosimilars, the prices of branded and biosimilars infliximab and etanercept decreased (Table 2).

Regression analysis indicated that the overall utilisation of individual bDMARDs in rheumatology specialities in UK hospitals changed by varying amounts between March 2014 and February 2017. There was a statistically significant increase in average monthly utilisation of bDMARDs for; adalimumab 0.48% (95% CI 0.22 to 0.75), certolizumab pegol 1.90% (95% CI 1.54 to 2.26), golimumab 3.06% (95% CI 2.46 to 3.65), abatacept 2.97% (95% CI 2.55 to 3.39) and tocilizumab 2.24% (95% CI 1.95 to 2.53), but not statistically significant for etanercept 0.04% per month (95% CI -0.21 to 0.30). In contrast, the overall utilisation of infliximab decreased slightly on average by 0.03% per month (95% CI -0.25 to 0.18) (Figure 1). Adalimumab (Humira®) and etanercept (Enbrel® and Benepali®) accounted for approximately 65% of bDMARDs market during the study period. The utilisation of branded infliximab (Remicade®) and etanercept (Enbrel®) decreased gradually since the launch of infliximab and etanercept biosimilars in March 2015 and March 2016 respectively, while, the utilisation of infliximab biosimilars (Inflectra® and Remsima®) and etanercept biosimilar (Benepali®) increased gradually achieving 58% and 48% of infliximab and etanercept market respectively by February 2017 (Figure 1). Similarly, expenditure on branded infliximab and etanercept decreased since the introduction of their biosimilars (Table 2).

Table 2 Price/DDD, utilisation and expenditure of branded and biosimilar adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab in rheumatology specialities in UK hospitals between March 2014 and February 2017

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Price/DDD (£s)** | **Utilisation (DDDs)** | **Expenditure (£s)** |
| **Molecule** | **Product** | **2014** | **2015** | **2016** | **Mar 2014 – Feb 2015** | **Mar 2015 – Feb 2016** | **Mar 2016 – Feb 2017** | **Mar 2014 – Feb 2015** | **Mar 2015 – Feb 2016** | **Mar 2016 – Feb 2017** |
| **Infliximab** | **Remicade®** | 16.67 | 15.94 | 13.14 | 2,039,765 | 1,900,393 | 1,157,549 | 34,019,560 | 30,306,550 | 15,215,980 |
| **Inflectra®** |  | 9.68 | 7.97 |  | 125,693 | 312,095 | - | 1,217,880 | 2,488,258 |
| **Remsima®** |  | 9.40 | 6.82 |  | 57,198 | 602,880 | - | 537,942 | 4,111,877 |
| **Etanercept** | **Enbrel®** | 24.92 | 24.92 | 21.22 | 4,899,762 | 5,180,622 | 3,933,930 | 122,102,081 | 129,102,215 | 83,480,003 |
| **Benepali®** |  |  | 15.91 |  |  | 984,224 | - | - | 15,662,107 |
| **Adalimumab** | **Humira®** | 25.38 | 25.33 | 25.33 | 5,004,910 | 5,486,896 | 5506,827 | 127,072,123 | 139,003,517 | 139,508,411 |
| **Certolizumab pegol** | **Cimzia®** | 24.87 | 24.93 | 24.98 | 649,728 | 809,257 | 909,328 | 16,161,700 | 20,178,376 | 22,720,818 |
| **Abatacept** | **Orencia®** | 36.57 | 36.57 | 36.57 | 280,907 | 395,212 | 440,885 | 8,149,257 | 12,053,430 | 13,903,016 |
| **Tocilizumab** | **RoActemra®** | 24.11 | 24.11 | 24.11 | 883,518 | 1,164,111 | 1,334,064 | 21,424,383 | 27,808,275 | 31,830,038 |
| **Golimumab** | **Simponi®** | 23.41 | 23.41 | 23.41 | 780,045 | 1189,186 | 1,299,277 | 18,704,728 | 26,826,999 | 27,641,862 |

DDD, defined daily dose. Price/DDD and expenditure measured in British pounds sterling

* 1. **Annual savings from the introduction of infliximab and etanercept biosimilars**

Table 3 shows that in the first year in which infliximab biosimilars were introduced (March 2015 to February 2016), there was a saving of £2,665,972 of which £1,373,001 can be attributed to the Remicade® price reduction, with the remainder coming from initiating new patients and switching existing patients on Remicade® to Inflectra® (£877,422) and Remsima® (£415,548). The total savings increased to £12,732,860 during the second year (March 2016 to February 2017) with a further price reduction of Remicade® contributing £4,080,361 and new patient initiation and switches to Inflectra® and Remsima® contributing £2,714,365 and £5,938,132 savings respectively (Table 3). In the first year in which etanercept biosimilar was introduced (March 2015 to February 2016) there was a saving of £23,418,287 of which Enbrel® price reduction contributed £14,553,532 savings (Table 3).

Table 3 Savings following the launch of infliximab and etanercept biosimilars and the price discounts compared to branded price before launch of biosimilar versions

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Mar 2015- Feb 2016** | **Mar 2016 -Feb 2017** |
| **Molecule** | **Product**  | **Savings\* (£s)** | **% price reduction** | **% market share for the molecule** | **% overall expenditure reduction for the molecule** | **Savings\*****(£s)** | **% price reduction** | **% market share for the molecule** | **% overall expenditure** **reduction for the molecule** |
| **Infliximab** | **Remicade®** | 1,373,001 | 4.37% | 91% | 6.76% | 4,080,361 | 21.17% | 56% | 36.8% |
| **Inflectra®** | 877,422 | 42% | 6% | 2,714,365 | 52.18% | 15% |
| **Remsima®** | 415,548 | 43.6% | 3% | 5,938,132 | 59 % | 29% |
| **Etanercept** | **Enbrel®** | - | - | - | - | 14,553,532 | 14.85% | 80% | 19.10% |
| **Benepali®** | - | - | - | 8,864,754 | 36.15% | 20% |

\* Savings measured in British pounds sterling

* 1. **Segmented regression of interrupted time series**

**3.3.1. Pre‐biosimilars market phase (March 2014‐February 2015)**

The trend of interrupted time series analyses (Table 4) indicates that the monthly utilisation of all bDMARDs (with the exception of branded infliximab) rose before the introduction of infliximab biosimilars in March 2015, as shown by the change in slope β1. This monthly increase was statistically significant for all bDMARDs. Monthly utilisation of branded infliximab (Remicade®) decreased significantly before the marketing of infliximab biosimilars (Table 4 and Figure 2).

**3.3.2. Post‐infliximab biosimilars market phase (March 2015‐ February 2016)**

The change in trend (β3) (Figure 2) showed a statistically significant increase in utilisation of infliximab biosimilars (Inflectra® and Remsima®) and a significant negative impact on the utilisation of the brand Remicade® (Table 4 and Figure 2). The trend for the other brands (Humira®, Enbrel®, Cimzia®, Orencia®, RoActemra® and Simponi®) did not change significantly in response to the introduction of infliximab biosimilars (Table 4). Similarly, the change in level (β2) of all bDMARDs (with the exception of RoActemra® and Simponi®) did not change significantly (Table 4).

**3.3.3. Post-etanercept biosimilar market phase (March 2016- February 2017)**

Once etanercept biosimilar (Benepali®) was available, there was a significant increase in the utilisation trend (β5) of Benepali® and Remsima® (infliximab biosimilar), and a corresponding significant negative impact on the trend of utilisation (β5) of etanercept brand Enbrel® (Figure 3), infliximab brand Remicade® (Figure 2) and infliximab biosimilar Inflectra®. The trend of utilisation of Humira®,Cimzia®, Orencia®, RoActemra® and Simponi® didnot change significantly in response to the introduction of etanercept biosimilars (Table 4). The level (β4) of utilisation of infliximab biosimilars (Inflectra® and Remsima®) increased significantly.

Table 4 Interrupted time series regression analysis of change in the utilisation of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab in rheumatology specialities in UK hospitals

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Infliximab(Remicade®)Coeff. (95% CI) | Biosimilar infliximab (Inflectra®)Coeff. (95% CI) | Biosimilar infliximab (Remsima®) Coeff. (95% CI) | Etanercept (Enbrel®)Coeff. (95% CI) | Biosimilar etanercept (Benepali®)Coeff. (95% CI) | Adalimumab (Humira®)Coeff. (95% CI) | Certolizumab (Cimzia®) Coeff. (95% CI) | Abatacept (Orencia®)Coeff. (95% CI) | Tocilizumab (RoActemra®)Coeff. (95% CI) | Golimumab (Simponi®)Coeff. (95% CI) |
| β1(Slope) | -1919 (-3667 - -171) \* | - | - | 3964(-621 - 8550) \* | - | 5100 (255 - 9945) \* | 1323 (497 - 2148) \* | 719 (363 - 1075) \* | 1058 (123 - 1994) \* | 2280 (848 - 3713) \* |
| β2(level) | 21130 (3973 - 38287) | - | - | 27445(-17565- 72457) | - | 21123 (-26430 - 68677) | 765 (-7333 - 8864) | 1245 (-2250 - 4742) | 9400(217 - 18583) \* | 18182 (4119 - 32246) \* |
| β3(Slope) | -1494 (-3966 - 977) \* | 2037(1406 - 2669) \* | 1077(506 - 1648) \* | -7916 (-14401 - -1430)  | - | -6486 (-13338 - 365)  | -515 (-1682 - 651) | -54.8 (-558 - 448) | 196 (-1126 - 1519) | -1762 (-3789 - 263) |
| β4(level) | -4781(-21938- 12375) | 10138 (3939 - 16336) \* | 8840 (3239 - 14440) \* | 33221 (-11790 - 78232) | - | -4149 (-51703 - 43404) | 3844 (-4254 - 11942) | -2600 (-6097 - 895) | 2818 (-6364 - 12001) | -1431 (-15494 - 12632) |
| β5(Slope) | -2486 (-4958- -13.9) \* | -2931(-3825 - -2038) \* | 3646(2839 - 4453) \* | -13797(-20283- -7311) \* | 20389(16766 - 24012) \* | 3452 (-3399 - 10304) | -799 (-1966 -366) | -241 (-745 - 262) | -571 (-1894 - 751) | 675 (-1351 - 2701) |

*Coeff., coefficient. Coefficient units are in defined daily doses (DDDs). β1 is the change in slope of the utilisation trend before launch of infliximab biosimilars (Inflectra® and Remsima®); β2 is the change in level of utilisation after launch of infliximab biosimilars (Inflectra® and Remsima®) and β3 is the change in slope of the utilisation trend after the launch of infliximab biosimilars (Inflectra® and Remsima®). Β4 is the change in level of utilisation after launch of etanercept biosimilar (Benepali®) and β5 is the change in slope of the utilisation trend after the launch of etanercept biosimilar (Benepali®). Numbers in parentheses are p-values. \* p-value <0.05 (significant)*

1. **Discussion**

Previous studies on the budget impact of infliximab and etanercept biosimilars have only estimated the potential savings resulting from the introduction of these biosimilars in different specialities at national and international levels [24-31]. Our study is the first analysing the actual impact of the introduction of these biosimilars on the utilisation of all bDMARDs in UK hospital rheumatology specialties and the subsequent savings realised.

A survey of the literature revealed that previous studies which analysed the budget impact of infliximab biosimilars have used models from the healthcare commissioner or payer perspective over a 3 – 5 years’ period and assumed that the price of infliximab biosimilars would range between 10-30% lower than that of branded Remicade® [24-29]. Jha et al., (2015) study estimated that cost savings from introduction of infliximab biosimilars for the treatment of all autoimmune diseases in the UK would be £3.21 - £9.63 million during the first year [24]. A model based in the Irish healthcare system in 2013, assumed that all RA patients on infliximab would be switched to infliximab biosimilars, with predicted cumulative savings of over £4.7 million in 5 years [25].

Our study shows that the actual annual cost saving from the introduction of infliximab biosimilars in rheumatology specialities was only £2.6 million in the first year which resulted in a reduction in the total annual expenditure on infliximab by 6.76%. This figure is lower than Jha et al’s., (2015) predicted savings (£3.21M - £9.63M) over all autoimmune diseases in the UK [24], since our study only covered rheumatology specialties. These real-world savings resulted from marketing Inflectra® and Remsima® at prices 42.4% and 21.14% lower than that of Remicade® with further reductions to 42% and 43.6% respectively (Table 3), which is greater than predicted by Jha et al., [24]. Furthermore, there was also a price reduction of Remicade® by 4.37% probably in response to the biosimilar competition, which had not been built in to Jha et al’s., model. Despite the larger than predicted price discounts, the first-year savings in UK hospitals as a result of the introduction of infliximab biosimilars were lower than predicted. This probably reflects the lower use of infliximab in rheumatology specialties compared to other autoimmune diseases [34] and the slow uptake of the biosimilars in the first year (Remicade® 91%: Inflectra® 6%: Remsima® 3%) (Table 3). Interestingly the second-year savings increased to £12.7 million and reduced the overall expenditure on infliximab by 36.8%, as a result of further price reductions of Inflectra® and Remsima® by 52.18% and 59% respectively compared to the Remicade® price in 2014 and an increase in the utilisation of infliximab biosimilars (Inflectra® 15%: Remsima® 29%) (Table 3). Furthermore, the price of Remicade® also reduced by 21.17% in response to the reduced cost of biosimilars which also contributed to the overall savings. These additional price discounts and increased use of infliximab biosimilars resulted in actual second year savings in UK hospitals closer to the savings predicted by Jha et al., [27-29].

A study by Ruff et al., (2015) estimated the five-year budget impact of etanercept biosimilars in the UK would result in savings of £100-£260 million based on the assumption that the etanercept biosimilar price would range between 10-25% lower than that of Enbrel® [30]. As with all budget analysis models, these analyses are subject to limitations, with the potential for input data to differ from real-life situations.

We found that the actual cost saving from the introduction of etanercept biosimilar in the first year was £23.4 million and reduced the overall expenditure on etanercept by 19.10%. This saving, in line with the predictions of Ruff et al., (2015) study [30] was a result of the marketing of the etanercept biosimilar Benepali® at a price 36.15% lower than that of Enbrel® and a price reduction of Enbrel® by 14.85%. As a result, there was a change in utilisation pattern of etanercept to 80% Enbrel®: 20% Benepali® (Table 3). This greater uptake of etanercept biosimilar in the first year may reflect the greater experience of rheumatologists with this molecule and increased confidence in bDMARDs biosimilars as a result of previous experience with infliximab [34]. These changes resulted in cumulative cost savings from the introduction of infliximab and etanercept biosimilars of £38.8 million in two years in rheumatology specialities in UK hospitals (Table 3).

Our study has shown that the impact of the introduction of infliximab biosimilars resulted in lower cost savings than estimated savings in previous studies in UK in the first year, but savings similar to those predicted in second year. This is likely to be due to the slower than predicted uptake of infliximab biosimilars in the first year, since infliximab biosimilars were the first approved bDMARDs in UK and as such may take time to diffuse and to be adopted by physicians/prescribers (Table 3). Also, in the past, the UK market has been one of the slowest markets in Europe to take up new medications such as biosimilar bDMARDs [35]. The initial successful experience with infliximab biosimilars probably resulted in their increased utilisation during the second year and the faster uptake of etanercept biosimilar.

Previous studies overestimated the uptake of infliximab biosimilars, but did not take into account the effect of competition between the reference medicine and the biosimilars and between biosimilars themselves. The competition between Remicade® and infliximab biosimilars resulted in price reductions of Remicade® by 4.37% in first year of the introduction of infliximab biosimilars and 21.17% in the second year (Table 2). Similarly, the competition between Inflectra® and Remsima® resulted in further price reductions in comparison with Remicade® from 42% to 52.18% for Inflectra® and 43.6% to 59% for Remsima®. This competition and price reduction resulted in increased utilisation of the less expensive biosimilar (Remsima®) and increased infliximab market share to 29% (Table 2). A further infliximab biosimilar (Flixabi®) was approved in mid-2016 by the European Medicine Agency and may in time increase competition in the infliximab marketplace and lead to further price reductions [36]. Similar competition was evident between Enbrel® and Benepali® (Table 2). Our analysis showed that the introduction of infliximab and etanercept biosimilars was associated with considerable savings, and the main drivers for this saving were the price discounts from both the originator and the biosimilars, and the number of patients prescribed the biosimilars (this analysis assumed the same the prevalence and incidence of rheumatic disease during the study period). In addition to the cost saving, biosimilars have the potential to expand stakeholders (patients and prescribers) choices, potentially increasing patient access to the same molecule or other medicines [37 -39]. The IMS Health report in 2016 indicated that the use of biologic medicines has doubled following the availability of biosimilars in the Europe [39].

Segmented regression was used to identify the impact of the introduction of infliximab and etanercept biosimilars on the utilisation of bDMARDs. Before the introduction of infliximab biosimilars, branded adalimumab (Humira®) and etanercept (Enbrel®) were the market dominants (Figure 1). This is in line with other reports that indicated that Humira® and Enbrel® were market leaders in RAas they were the first to market bDMARDs for self-administration in 2000 and 2003 respectively [40].Monthly growth of Humira® was higher than Enbrel®, certolizumab pegol (Cimzia®), abatacept (Orencia®), tocilizumab (RoActemra®) and golimumab (Simponi®). In contrast, Remicade® utilisation was decreasing even before the availability of infliximab biosimilars as shown in the interrupted time series analysis (Table 4). These findings suggest that prescribing decisions were based on prescribers/patient preferences for the more convenient agents; infliximab has to be administered by intravenous infusion in a hospital setting or via home care companies, whereas other agents can be self-administered subcutaneously with user friendly, ready to use prefilled syringe and pens. These results support the findings of studies on patient preferences for subcutaneously administered bDMARDs and physicians’ preferences in UK and USA [41-43]. These are closely intertwined, as Curtis et al., (2010) demonstrated in their study of bDMARDs which showed prescribers preferences heavily influenced patients’ decisions on choice of medicine when initiating treatment for RA [44]. Furthermore, Augustovski et al’s (2013) study showed that the choice of biologic treatment for RA patients depends on cost, systemic adverse events, frequency of administration, efficacy, route of administration, local adverse events and serious infections [45].

The introduction of infliximab biosimilars resulted in further reductions in the utilisation of the brand Remicade® but did not appear to have influenced the utilisation of other branded bDMARDs significantly (Table 4). Despite the small price difference between infliximab biosimilars (Inflectra® and Remsima®), monthly growth (β3) of the less expensive biosimilar Inflectra® was higher than Remsima® in the firstyear but this was reversed in year two when Remsima® price was lowered than Inflectra®. These results suggest that the prescribing decisions were initially based on prescribers/patient preferences among bDMARDs but then based on price when selecting between the brand and biosimilars of the same molecule and between the biosimilars themselves. This is at variance with Kim et al’s findings in South Korea that showed that the introduction of infliximab biosimilars significantly decreased the utilisation of branded etanercept and adalimumab in South Korea [46] suggesting that cultural or other factors may be in play.

With the availability of less expensive etanercept biosimilar in March 2016, the utilisation of Enbrel® reduced with a growth in the utilisation of Benepali® (Table 4). Again, the introduction of etanercept biosimilar appeared not to have significantly influenced the utilisation of other branded bDMARDs (Table 4). Interestingly, the utilisation of Remsima® increased (Figure 1 and Table 4), most likely in response to a price reduction in Remsima® which made it the least expensive infliximab. This marked price reduction of Remsima® between March and April 2016 was responsible for shifting prescribing of infliximab biosimilars from Inflectra® to Remsima®, which is demonstrated in the significant increase in the level (β4) of Inflectra® before this price change followed by a significant decrease in trend (β5) of utilisation of Inflectra® as a result of price change.

This further reinforces our findings that historically prescribing decisions for different bDMARDs were based on prescribers/patient preferences but based on price when selecting between the brand and biosimilars of the same molecule.

The strengths of this study were that we were able to analyse the actual utilisation patterns of all available bDMARDs in rheumatology specialties in UK hospitals following the introduction of biosimilars. Whilst rituximab is an option in the treatment of RA when other biologics have failed no DDD index have been established for rituximab due to its highly-individualised utilisation and wide dosage ranges [47]. Therefore, rituximab utilisation cannot be compared to other bDMARDs and has not been included in this study. A limitation was that the time period for analysis was limited to 3 years as we could only access monthly data for secondary care since 2011. As data was only available at gross national level and not individual patient level it was not possible to distinguish how much utilisation of biosimilars was initiation or switching. Whilst interrupted time series regression analysis is regarded as the gold standard in pharmaco-epidemiological studies such as this one, there are methodological issues which need to be considered. Seasonality in the data can be a confounding variable. The medicines considered in our study are chronic treatments for autoimmune rheumatological disorders. Therefore, seasonal variation in use is unlikely. Another issue is autocorrelation of data. To adjust for this effect, we applied the autoregressive integrated moving average (ARIMA) function within the statistical software to undertake the interrupted time series regression analysis.

1. **Conclusion**

This study has shown that the introduction of bDMARDs biosimilars in UK hospitals has resulted in considerable cost savings to the NHS. It has also shown that the bDMARDs market has reacted in a complex way to the availability of biosimilars due to the branded products reducing their prices in response to the availability of less expensive biosimilars, then price competition between the biosimilars themselves. Whilst not unexpected, the price changes could not be accurately predicted in previous studies modelling the impact of biosimilars. The availability of biosimilar bDMARDs has not impacted significantly on other branded bDMARDs molecules. This suggests that when a biosimilar is available for a directly comparable branded molecule, price is the key influencing factor in its prescribing.

**Compliance with ethical standards**

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**Informed consent:** No informed consent was required for this research.

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Fig.1 Monthly utilisation of bDMARDs in UK hospitals between March 2014 and February 2017

Fig. 2 Utilisation of branded infliximab (Remicade)® and segmented regression results before and after the introduction of infliximab and etanercept biosimilars

Fig. 3 Utilisation of branded etanercept (Enbrel)® and segmented regression results before and after the introduction of infliximab and etanercept biosimilars